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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
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EXAMINER

18M1/0319
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ART UNIT	PAPER NUMBER

1817

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DATE MAILED: 03/19/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 12/10/96

☒ This action is FINAL.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

- ☒ Claim(s) 6, 7, 10, 13 and 16-18 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 6, 7, 10, 13 and 16-18 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

- ☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been
☐ received.
☒ received in Application No. (Series Code/Serial Number) 08/182550
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- ☐ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s) _____
☐ Interview Summary, PTO-413
☐ Notice of Draftsperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

—SEE OFFICE ACTION ON THE FOLLOWING PAGES—

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CHANGE IN ART UNIT

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1817.

AMENDMENT ACKNOWLEDGED

The amendment filed December 10, 1995 (paper #9) under 37 CFR 1.115 is acknowledged and has been entered. Claims 13, 16, 6 and 7 have been amended. Claims 14, 15 and 8 have been cancelled. Claims 6, 7, 10, 13 and 16-18 are pending.

INFORMALITIES

The drawings are objected to for reasons of record (see PTO-948 attached to paper #7). Correction is required before or at the determination of patentable subject material.

PRIOR CITATION OF TITLE 35 SECTIONS

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

THE INVENTION ACCORDING TO APPLICANT

According to applicant,

[t]he invention is the discovery that the use of a controlled amount of microparticles and a controlled amount of sample will allow for improved measurement of the concentration of an analyte in a sample (where the samples will typically have a concentration within a certain range). The amount of microparticles and the amount of sample must be determined by experimentation using samples having a known concentration of analyte where the concentration is within a "typical" range. *This experimentation is carried out during development and production. It is not assumed that the user is required or needs to do this.* (response paper #9, page 6, ¶2)

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According to the invention, the range and sensitivity are adjusted by selecting the sample volume and particle number to obtain a relevant working range. The result is read from an individual microparticle (although more than one measurement of concentration using an individual microparticle may be made to ensure statistical reliability). (response paper #9, page 8, ¶1),

In distinction over the prior art, applicant maintains

...the Soini patent does not [t]each or suggest to a person of ordinary skill in the art that very low analyte concentrations can be assayed by **decreasing** the amount of microparticles. The person of ordinary skill in the art would not, with a reasonable expectation of success, have been motivated to modify the method described in the Soini patent by **decreasing** the amount of microparticles. In assays known prior to the present invention it was normal routine to **increase** the binding surface when small amounts of analytes were to be measured. The immunoassay method of the present invention, therefore, is not a matter of routine optimization. The "optimization" method according to the present invention (the adjustment of amount of microparticles and sample volume used so as to achieve an easily detectable signal strength from an individual microparticle) is an entirely new idea which has never been described before. (emphasis in the original, response paper #9, ¶ bridging page 10-11)

THE PROBLEM

The major problem is that the claim language reciting fails to suggest using **decreased** amounts of microparticles *vis-a-vis* the prior art.

Recitation of "predetermined" amounts of sample and bioaffinity reactant A-coated microparticles with luminescent-labelled bioaffinity reactant B reads on routine optimization of a basic immunoassay.

The requirement that after the specific binding reaction, "each individual microparticle emits a signal strength that corresponds to the analyte in the sample" simply requires the

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signal from each measured microparticle to contribute to the signal from which analyte concentration is calculated.

The requirement for individual microparticle measurement limits the signal detection means. Admittedly, "[i]ndividual microparticles can be assayed with e.g. a flow cytometer, time-resolved microscope or time-resolved microfluorometer or with other measuring instruments based on the use of time-resolved technology (US 5,028,545; Seveus L et al., Cytometry 13: 329-338 (1992))." (specification page 10, lines 1-5)

Recitation of "determining the analyte concentration...by comparing said signal strength measured from said individual microparticles with a standardization curve..." does not clearly limit sample determination to the signal from a single microparticle. Applicant has indicated that "more than one measurement of concentration using an individual microparticle may be made to ensure statistical reliability" (response paper #9, page 8, ¶1). Indeed, if the result is not reliable, the utility of the assay becomes questionable. Therefore, it appears inherent that a sufficient number of microparticle signals be measured to provide a usable result.

The other problem is that inherent in this discussion are two other specific binding partners, i.e. bioaffinity reactants A and B, whose characteristics, e.g. average coating density on a microparticle, average amount of labels conjugated thereto, relative binding affinities, etc. also influence the "optimization" of the immunoassay.

REJECTIONS UNDER 35 USC 112

Second Paragraph

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Claims 6, 7, 10, 13 and 16-18 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant has failed to claim what he regards as his invention, i.e. very low analyte concentrations can be assayed by **decreasing** the amount of microparticle over what is conventionally used in the prior art. See the discussion above.

Thus, the "improvement" step of claim 13 is still unclear. It is unclear whether analyte concentration is determined from a single microparticle measurement *or* whether an average signal obtained by measuring a predetermined number of individual microparticles is used such that signal measurements fall within a proscribed acceptable variance. Applicant states "each of the individual microparticles is **not** separately measured" (emphasis added, response paper #9, sentence bridging pages 4-5). However, claim 13 fails to state clearly what is being measured, especially in relation to the "predetermined number of microparticles" reacted with sample in the "contacting" step, e.g. one/some/all of these microparticles.

First paragraph

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure and failing to provide an adequate written description of the invention.

By way of further clarification, the objection in paper #7, page 5, lines 6-9 was that the specification did not teach/suggest how to determine analyte concentration based upon the signal from single, isolated, individual microparticle. The examiner does not dispute that

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optimizing the amount of reactants, including sample, solid phase antibody and labelled immunoreactant is more than routine experimentation.

The objection in paper #7, page 5, line 10 to page 6, line 2, is withdrawn upon further consideration. However, not all of applicant's arguments are agreed with. According to the specification:

In a competitive immunoassay

[t]he amount of the microparticles and of the analyte-specific antibody coated onto them will be adjusted to a minimal sample volume to allow a replacement (of labelled analyte by the analyte to be assayed) of 75 - 95% at the highest sample concentration. This still allows the remaining signal strength to be reproducibly measured...from the surface of individual microparticles, and at the same time, the signal strength (due to the specific binding of labelled analyte to the coated microparticle) corresponding to the lowest analyte concentration *will not exceed the binding capacity of individual particles*. The measuring range is adjusted...by altering the amounts of the microparticles and antibodies used in the assay method in such a manner that measurements can always be taken from individual microparticles. (emphasis added, page 8, lines 17-33)

In a non-competitive immunoassay

[t]he amount of the microparticles used in the assay, coated with the analyte-specific antibody or bioaffinity reactant as well as the amount of analyte per microparticle will be adjusted so that a minimal concentration and volume of the analyte will contain *enough analyte for binding* to the surface of individual microparticles, and enough for measurement from individual microparticles by means of a labelled specific antibody (labelled bioaffinity reactant) and with the sensitive label technology used. The measurement range required and the sensitivity of the measurement will be controlled by adjusting the amount of microparticles used in the assay and by adjusting sample volume, if needed. (emphasis added, page 9, lines 21-33)

with a smaller amount of microparticles the ... (analyte) in the sample will be bound in a higher concentration onto the surface of individual microparticles; the sensitivity of the assay and the measurement range may be controlled, if

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needed, by the amount of the microparticles and the sample volume, so as to allow measurement from individual microparticles. The reproducibility of the assay can be improved by measuring a greater number of individual microparticles. (page 12, lines 6-17).

5 Thus, it is respectfully submitted that a relationship between the analyte and the available binding sites on the microparticles exist. Consequently, although the relative amounts of reactants must be optimized in terms of binding sites and signal strength, it is agreed that this is within routine experimentation.

10 The objection regarding DELFIA is withdrawn as the record now indicates that DELFIA is a recognized term of art.

The objection regarding "sensitive label technology" is withdrawn since the record clearly indicates that luminescent labelled affinity systems are being referred to.

15 The objection regarding how the claimed invention differs from routine optimization is maintained. Applicant has failed to present any reasoned argument as to why routine optimization would not suggest using as small an excess of solid phase reactant as possible to prevent unnecessarily "diluting" the signal of later bound labelled reactant (to say nothing about cost considerations, etc.). Applicant simply states this "is not true for particle-based assays" (response paper #9, page 10, ¶3). Secondly, applicant argues this is NOT optimization because the skilled artisan would NOT optimize by DECREASING (presumably 20 the already optimized) amount of microparticles being used. Rather the skilled artisan would INCREASE the binding surface when small amounts of analytes were to be measured. It is respectfully submitted that routine optimization would recognize use of microparticles would

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inherently provide an enhance binding surface; and, that the skilled artisan would not spread a low concentration analyte over so large a surface area as to render analyte-specific label indistinct from non-specific label binding. The specification fails to provide any comparison between the minimum surface binding characteristics of the prior art and those of the instant invention.

Finally, the objection regarding "wet"/"dry" differentiation is withdrawn in view of applicant's comments.

Claims 6, 7, 10, 13 and 16-18 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

REJECTIONS UNDER 35 U.S.C. § 103 (a)

Claims 6, 10, 13 and 16-18 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Soini et al. (US 5,028,545) alone or as necessary further in view of either Ekins et al. (*Clinical Chemistry*, 37(11):1955-1967 (1991)) or Buechler et al. (US 5,089,391) for reasons of record (see paper #7, pages 7-9).

Claim 7 is rejected under 35 U.S.C. § 103(a) as being unpatentable over the references as applied to claim 13 above, and further in view of Bush et al. (*Analytical Biochemistry*, 202:146-151 (1992)) for reasons of record (see paper #7, pages 7-9).

Traversal/Response

Applicant argues Soini et al. only describes performing a multiparameter assay in a flow cytometer by recognizing batches of particles of different categories. Soini et al. does not teach decreasing the amount of microparticles.

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Insofar as "relative" amounts of microparticles are not specified in either Soini et al. or the claimed invention, argument is not persuasive because it is not commensurate in scope with the claimed invention. Moreover, it is respectfully submitted that several cites in Soini et al. do teach and/or suggest the claimed invention. Specifically, Soini et al. states

5 In this invention the sample is including all different analytes is first incubated with a pool of microspheres and with a pool of labelled reactants **in the smallest possible volume** (for example 10-100 μ l) in order to achieve a complete reaction in a short time. ... A sufficient number of microspheres are
10 analyzed and the fluorescence signals from **each microsphere** are registered in a computer. (emphasis added, col. 2, lines 20-37).

and refers to

measuring the concentration of the analyte **on each microsphere**.
(emphasis added, col. 1, lines 53-56)

Applicant also argues Ekins et al. is based upon the theory of fractional occupancy
15 which is totally different than the theory of the instant invention (see Appendix 5 attached to paper #9); and, proposes a "compact disc" format which no one has been able to reproduce. Finally, applicant argues that sensitivity does not change the design of an assay and, therefore, the discussion of the teachings found in Ekins et al., whether drawn to the Yalow-Bernson theory or the fractional occupancy theory are "not believed to be relevant to the issue of
20 *prima facie* obviousness" (response paper #9, page 15, ¶3).

First, the examiner is not taking any position as to the theoretical basis of applicant's invention. Whether the Yalow-Bernson theory or the occupancy theory is followed is of no moment since each theory provides definable criteria for optimizing sensitivity, etc. Ekins et al. provides a description of both theories as well as their criteria for maximizing sensitivity,

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etc. (although Ekins et al. naturally enough prefers their own theoretical basis). Secondly, applicant's opinion that Ekins et al. is irreproducible is without support and appears contray to applicant's later assertion that, "It is generally acknowledged that Ekins is correct" (response paper #9, page 15, ¶3). Finally, it is respectfully submitted that "sensitivity" is relevant to the
5 issue of obviousness because an analyte cannot be measured at low concentrations if the assay is not sensitive enough to measure analyte distinguishably from background/non-specific binding at those low concentrations. Thus, criteria useful for maximizing sensitivity are relevant to assay design.

Applicant argues Buechler et al.'s teachings of how to optimize an assay to provide
10 detectable results at a above a preselected analyte threshold concentration is entirely different from the claimed invention's measurement of an analyte within a predetermined, clinically relevant concentration range.

The relevancy of this argument is unclear. It would seem that a "predetermined, clinically relevant concentration range" would have a minimum threshold concentration by
15 virtue of it encompasses a "range" of concentration. Secondly, there are no claimed limitations as to detectable analyted concentration ranges, sensitivity, specificity, etc. Therefore, this argument is not convincing.

Applicant argues Bush et al. measures total microparticles, i.e. Bush et al. "merely describes a conventional use of a microparticle suspension to read the result from a PCR
20 amplification-based DNA hybridization assay."

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As stated in the last Office action, Bush et al. is added to show the applicability of time-resolved fluorescent labelled microparticle based assays to hybridization formats.

Applicant has not disputed that Bush et al. provides a reasonable expectation of success in applying the teachings of the references in a hybridization format.

5 Applicant has argued each reference individually. Merely pointing to a difference between the claimed invention and one of the references is not persuasive of error in the obviousness conclusion evinced by the combined disclosures of the applied prior art. Furthermore, it is axiomatic that the entire disclosure of a reference must be evaluated. Finally, where the general conditions of a claim are disclosed in the prior art, discovering the
10 optimum or workable ranges involves only routine skill in the art.

CONCLUDING REMARKS

In conclusion, applicant's amendments and arguments filed December 10, 1996 have been fully considered but are not deemed convincing of patentability for the above reasons and other reasons already of record. The claim language fails to recite using **decreased**
15 amounts of microparticles *vis-a-vis* the prior art. Moreover, the prior art, specifically Soini et al., suggests reacting sample, microspheres and labelled reactants in the smallest possible volume (for example 10-100 μ l) in order to achieve a complete reaction in a short time; as well as measuring the concentration of the analyte on each microsphere.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time
20 policy as set forth in 37 C.F.R. § 1.136(a).

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5 A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL
ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION.
IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE
MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT
10 MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED
STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE
ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE
PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING
DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD
FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS
FINAL ACTION.

Any inquiry concerning this communication or earlier communications from the
examiner should be directed to Carol A. Spiegel whose telephone number is (703) 308-3986.

15 If attempts to reach the examiner by telephone are unsuccessful, the examiner's
supervisor, Dr. Paula K. Hutzell, can be reached on (703) 308-4310. The fax phone number
for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or
proceeding should be directed to the Group receptionist whose telephone number is (703)
308-0196.

20 Carol A. Spiegel
March 14, 1997

Carol A. Spiegel
CAROL A. SPIEGEL
PRIMARY EXAMINER
GROUP 1800